

Model for calculating the risk of venous thrombosis

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Aim. To develop a model for calculating the risk of venous thrombosis, taking into account the presence of known risk factors, comorbidity and congenital thrombophilia.

Material and methods. During the study (2015 to 2017), 79 patients with venous thrombosis were examined (36 men and 43 women, mean age — 56,76±15,570). The control group consisted of 83 patients and healthy volunteers without thrombosis at the moment and in history (35 men and 48 women, average age — 43,95±18,136). All individuals included in the study were analyzed for the presence of G1691A mutations in the factor V gene, G20210A in the prothrombin gene, C677T polymorphism in the 5,10-methylene-tetrahydrofolate reductase gene, and polymorphism in the SERPINE1 gene of plasminogen activator inhibitor. Real-time polymerase chain reaction was used to identify mutations. To create a risk calculation model, a linear regression analysis was performed.

Results. We have developed a model for calculating the risk of venous thrombosis. The resulting formula showed high prognostic accuracy (the area under the ROC curve is 95,9%). For patients who do not have data on the presence of these mutations, a short version of the risk calculation model was developed (the area under the ROC curve is 94,6%).

Conclusion. We have developed a risk calculation model taking into account the presence of known risk factors, congenital thrombophilia and comorbidities. Thromboprophylaxis is necessary in >0,45 individual risk, which corresponds to a high risk of developing venous thrombosis. Patients who have not previously been diagnosed with thrombophilia and are in the middle risk group for venous thrombosis, according to a short version of the model,

must be screened for congenital thrombophilia to clarify the risk.

Key words: congenital thrombophilia, overweight, obesity, venous thrombosis of the lower extremities, pulmonary embolism, risk calculation model.

Conflicts of Interest: nothing to declare.

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According to the Global Burden of Disease Study, thromboses cause every fourth death in the world [1]. These data mainly belong in arterial thrombosis, and if venous thrombosis were taken into account, the statistics would be worse. Unfortunately, data on the prevalence and mortality from venous thromboembolism (VTE) are limited and available only in a few large regions. Every year, 10 million new cases of VTE are recorded worldwide. [2]. There are 300-600 thousand VTE-related deaths in the USA per year [3], in Europe — 544 thousand [4]. According to the Russian Phlebological Association, about 80 thousand new cases are annually registered in the Russian Federation [5]. The incidence of VTE has increased significantly over the past decades. That was revealed by population-based cohort study in Olmstead County (USA) [6].

The VTE development is influenced by a large number of factors. There are some predisposing acquired risk factors, such as traumas, surgery, cancer, chemotherapy, hormonal contraceptives and hormone replacement therapy, pregnancy, the postpartum period, immobilization, obesity, old age, etc. [7]. A significant risk factor for thrombosis is congenital thrombophilia [8].

Despite the high prevalence and mortality, VTE is preventable [9]. Proper prevention strategy can significantly reduce the VTE incidence. At the same time, anticoagulant use for prevention will increase the risk of bleeding, especially in elderly patients with severe concomitant pathology and highest risk of thrombosis [10].

We consider that our risk assessment model (RAM) for venous thrombosis can cover the maximum number of factors, and its use in practice will reduce the thrombosis risk and do not significantly increase the bleeding risk.

Material and methods

The study was conducted from 2015 to 2017. A total of 79 patients with venous thrombosis (36 men and 43 women, mean age $56,76 \pm 15,57$) who were diagnosed with pulmonary embolism and lower extremity superficial and deep vein thrombosis (44,3%), lower extremity deep vein thrombosis (2,9%) and pulmonary embolism of unknown origin (22,8%) were examined.

The control group consisted of 83 inpatients and healthy volunteers without thrombosis and history of it (35 men and 48 women, mean age — $43,95 \pm 18,14$).

The inclusion criteria were age over 18 years, the thrombosis, established at the moment or in the history, and completed informed consent. Exclusion

criteria were age up to 18 years, pregnancy and first 6 weeks of postpartum period, and cancer.

Diagnosis of thrombosis was carried out in accordance with modern Russian guidelines. During hospitalization, we collected data of medical history and physical, laboratory and instrumental tests. All participants were analyzed for the most common thrombophilia types: G1691A (Factor V Leiden) mutation, prothrombin G20210A mutation, polymorphism (C677T) in the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene, plasminogen activator inhibitor-1 (PAI-1) gene (SERPINE1) polymorphism. To detect mutations, real-time PCR was used.

The study was carried out in accordance with the standard of Good Clinical Practice and principles of Declaration of Helsinki. The study protocol was approved by the ethics committees of all participating medical centers. Prior to inclusion, all participants completed written informed consent.

Results

In a regression analysis, it was found that in order to predict venous thrombosis, it is necessary to assess data such as the patient's age, weight and height, and early deaths in the family history (Table 1). Risk factors for venous thrombosis are major trauma, surgery, and concomitant diseases, such as coronary artery disease (CAD), heart failure (HF) according to NYHA classification, chronic obstructive pulmonary disease (COPD) and exacerbation of inflammatory bowel disease. The duration of asthma, atrial fibrillation (AF) and diabetes are also important. Of congenital thrombophilia, the factor V Leiden and prothrombin G20210A mutations, and MTHFR C677T and PAI-1 polymorphisms were significant.

The risk of venous thrombosis is calculated as follows:

The risk of venous thrombosis = $-2,4813 + 0,1105 \times (\text{HF according to NYHA classification}) + 0,0031 \times (\text{weight}) + 0,0124 \times (\text{age}) - 0,2923 \times (\text{COPD}) - 0,1344 \times (\text{early deaths in the family history}) + 0,1960 \times (\text{factor V Leiden mutation}) + 0,0042 \times (\text{asthma duration}) + 0,2550 \times (\text{trauma}) + 0,0126 \times (\text{height}) + 0,3303 \times (\text{surgery}) + 0,2300 \times (\text{combination of mutations}) - 0,0041 \times (\text{AF duration}) - 0,0915 \times (\text{CAD}) + 0,2932 \times (\text{exacerbation of inflammatory bowel disease}) - 0,1853 \times (\text{MTHFR C677T polymorphism}) + 0,0018 \times (\text{diabetes duration}) + 0,1000 \times (\text{prothrombin G20210A mutation}) - 0,0101 \times (\text{polymorphism PAI-1})$, where:

- HF according to NYHA classification (0 — no HF, 1 — class I, 2 — class II, 3 — class III, 4 — class IV);
- weight, kg;
- age, years;

Table 1
**Regression coefficients
for predicting the venous thrombosis**

Factor	B	β
Constant	-2,481	–
HF according to NYHA classification	0,111	0,245
Weight (kg)	0,003	0,140
Age, years	0,012	0,441
COPD	-0,292	-0,458
Early deaths in the family history	-0,134	-0,095
Factor V Leiden Mutation	0,196	0,062
Asthma duration	0,004	0,114
Trauma	0,255	0,098
Height (cm)	0,013	0,220
Surgery	0,330	0,074
Combination of mutations	0,230	0,230
Duration of atrial fibrillation	-0,004	-0,113
Coronary artery disease	-0,092	-0,177
Inflammatory bowel disease	0,293	0,103
MTHFR C677T polymorphism	-0,185	-0,185
Diabetes duration	0,002	0,070
Prothrombin G20210A mutation	0,100	0,035
PAI-1 polymorphism	-0,010	-0,008

Note: B — non-standardized coefficients, β — standardized coefficients.

— COPD (0 — No COPD, 1 — Stage I: mild COPD, 2 — Stage II: moderate COPD, 3 — Stage III: severe COPD, 4 — Stage IV: very severe COPD);

— early deaths in the family history (0 — no, 1 — yes);

— factor V Leiden mutation (0 — no, 1 — yes);

— asthma duration, years;

— traumas in history (0 — no, 1 — yes);

— height, cm;

— surgeries in history (0 — no, 1 — yes);

— combination of mutations (0 — no, 1 — yes);

— AF duration, years;

— CAD (0 — No CAD, 1 — atherosclerotic cardiosclerosis, 2 — old myocardial infarction, 3 — stable angina, 4 — vasospastic angina);

— exacerbation of inflammatory bowel disease (0 — no, 1 — yes);

— MTHFR C677T polymorphism (0 — no, 1 — yes);

— diabetes duration, years;

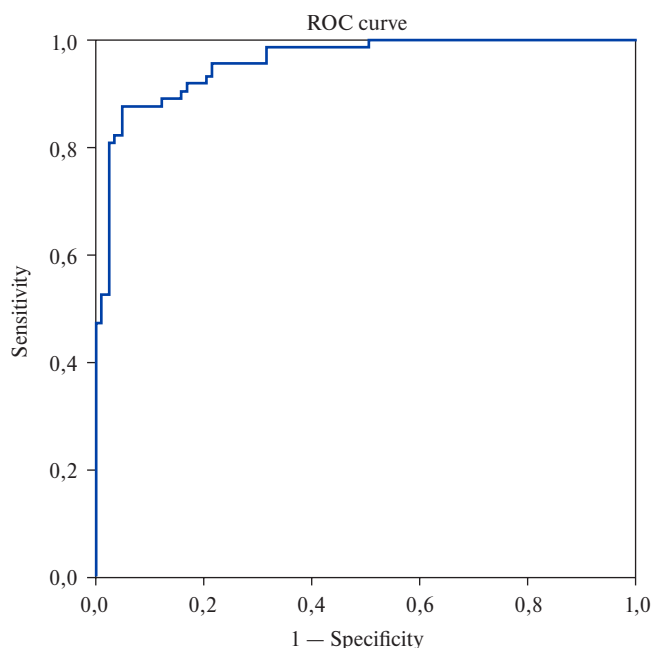


Fig. 1. ROC curve for predicting the venous thrombosis, taking into account congenital thrombophilia.

Note: area under the ROC curve — 95,9%

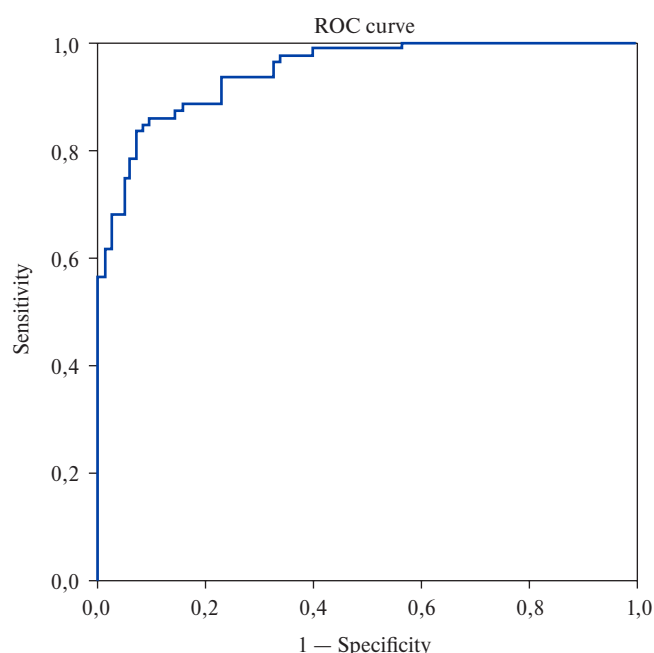


Fig. 2. ROC-curve for predicting the venous thrombosis without data on congenital thrombophilia.

Note: area under the ROC curve — 94,6%.

— prothrombin G20210A mutation (0 — no, 1 — heterozygous carriage, 2 — homozygous carriage);

— PAI-1 polymorphism (0 — no, 1 — yes).

This formula showed a sufficiently high forecast accuracy and clinical significance. To analyze the accuracy, the ROC curve was calculated (Fig. 1).

Table 2

Distribution of patients with venous thrombosis by risk groups

Risk groups for venous thrombosis		Thrombosis			
		No	Yes	Overall	Proportion, %
Low	up to 0,2615	50	1	51	2,0
Moderate	from 0,2615 to 0,45	24	7	31	22,6
High	from 0,45 to 0,627	7	12	19	63,2
Veri high	from 0,627	2	54	56	96,4

Low risk
 Moderate risk
 High risk
 High risk

Table 3

Risk levels of venous thrombosis in a virtual patient depending on the presence of mutations and increased BMI

Weight	BMI	No mutations	PAI-1	MTHFR + PAI-1	F2 G/A	F2 G/A + MTHFR	F2 A/A	F5 Leiden	F5 Leiden + MTHFR	F2 A/A + MTHFR	F2 G/A + PAI-1	F2 A/A + PAI-1	F5 Leiden + PAI-1	F5 Leiden + F2 G/A
Normal	23,44	0,14	0,13	0,18	0,24	0,29	0,34	0,34	0,38	0,39	0,46	0,56	0,56	0,67
Overweight	26,56	0,17	0,16	0,21	0,27	0,32	0,37	0,37	0,42	0,42	0,49	0,59	0,59	0,70
Class I obesity	30,86	0,21	0,20	0,24	0,31	0,35	0,41	0,41	0,45	0,45	0,53	0,63	0,63	0,74
Class II obesity	35,16	0,24	0,23	0,28	0,34	0,39	0,44	0,44	0,48	0,49	0,56	0,66	0,66	0,77
Class III obesity	41,02	0,29	0,28	0,33	0,39	0,44	0,49	0,49	0,53	0,54	0,61	0,71	0,71	0,82

Abbreviations: F2 A/A — homozygous mutation in the prothrombin gene, F2 G/A — heterozygous mutation in the prothrombin gene, F5 Leiden — factor V gene mutation, MTHFR — methylene tetrahydrofolate reductase gene, PAI-1 — mutation in the plasminogen activator inhibitor-1 gene.

Low risk
 Moderate risk
 High risk
 High risk

Further, to modify the risk into the probability of thrombosis, we formed 4 risk groups to calculate the joint distribution of risk and presence of thrombosis (Table 2). In our study, 2% of patients with thrombosis were in the low-risk venous thrombosis group, 22,6% in the moderate-risk group, 63,2% in the high-risk group, and 96,4% in the very high-risk group.

Here are a few examples to demonstrate how the calculator works. Let us suppose that a 35-year-old patient (height — 160 cm, weight — 58 kg, body mass index (BMI) — 22,66 kg/m²) has no congenital thrombophilia and concomitant pathology. In this case, RAM consider that the risk is 0,14. So, a patient has the low risk of venous thrombosis.

If a patient has excess body weight (height — 160 cm, weight — 68 kg, BMI — 26,56 kg/m²), the risk of venous thrombosis will be 0,17 (low risk); in case of

class I obesity (height — 160 cm, weight — 79 kg, BMI — 30,86 kg/m²) — 0,21 (low risk);); in case of class II obesity (height — 160 cm, weight — 90 kg, BMI — 35,16 kg/m²) — 0,24 (low risk). Only class III obesity will lead to moderate-risk of venous thrombosis — 0,29 (height — 160 cm, weight — 105 kg, BMI — 41,02 kg/m²). Consequently, in the absence of mutations, a patient is in the moderate-risk group of venous thrombosis only in class III obesity (Table 3).

If a patient is carrier of one mild mutation (for example, PAI-1 polymorphism), then the thrombosis risk depending on BMI will be about the same. In case of combination of two mild mutations (MTHFR C677T and PAI-1 polymorphisms) and class II obesity, a patient will go up to the medium-risk group.

Homozygous carriage of prothrombin G20210A and presence of factor V Leiden mutation will lead to a high risk of thrombosis in patients with class III obesity. Patients with combination of prothrombin G20210A or factor V Leiden mutations with MTHFR C677T polymorphism and normal weight or overweight will have the moderate risk of thrombosis, and in case of obesity, the risk will be high. In combination with PAI-1 polymorphism, the risk will be high in patients with normal weight and overweight, and in case of obesity, the risk will be very high. Patients with both prothrombin G20210A and factor V Leiden mutations will have very high risk for any body weight.

In addition to mutations and increased BMI, the thrombosis risk will be affected by age, the presence of CAD, HF, COPD, early deaths in family history, recent traumas and surgeries, inflammatory bowel disease, as well as the duration of asthma, AF and diabetes. So, if a patient with BMI=22,66 with a factor V Leiden mutation and PAI-1 polymorphism has type 2 diabetes for 3 years and asthma for 8 years, then the risk of venous thrombosis will be very high (0,63) even with overweight.

If a patient does not know about presence of the listed mutations, then it is possible to use a truncated RAM version (Table 4). The algorithm for calculating the risk of venous thrombosis is similar.

Using the current RAM, it is possible to calculate the individual risk of venous thrombosis (Table 5) and justify the need for thrombophilia screening to clarify the risk. For example, according to the truncated RAM version, a patient with class II obesity (height — 160 cm, weight — 90 kg, BMI — 35,16 kg/m²) will have moderate risk of thrombosis (0,32). In this case, screening for thrombophilia is required to clarify the risk of venous thrombosis.

However, the full version of the calculator has a higher forecast accuracy (the area under the

ROC curve — 95,9) compared to the truncated version (the area under the ROC curve — 94,6) (Fig. 2).

Both online RAM versions will be available at <http://1mgmu.com>.

Discussion

VTE is a serious medical problem worldwide [1]. The risk of thrombosis in a patient depends on individual factors. An accurate assessment of the thrombosis risk is sometimes difficult for practitioners. In order to determine the need for prevention, there are

Table 4
Regression coefficients for predicting the venous thrombosis by RAM version without thrombophilia

Factor	B	β
Constant	-2,488	0,224
HF according to NYHA classification	0,101	0,142
Weight (kg)	0,003	0,453
Age, years	0,013	-0,482
COPD	-0,312	-0,104
Early deaths in the family history	-0,148	0,103
Asthma duration	0,004	0,127
Trauma	0,334	0,22
Height (cm)	0,013	0,224
Surgery	0,332	0,074
Duration of atrial fibrillation	-0,005	-0,149
Coronary artery disease	-0,089	-0,174
Inflammatory bowel disease	0,345	0,131
Diabetes duration	0,009	0,074

Note: B — non-standardized coefficients, β — standardized coefficients.

Risk groups for venous thrombosis by RAM version without thrombophilia

Risk groups for venous thrombosis		Thrombosis			
		No	Yes	Overall	Proportion, %
Low	up to 0,32	55	2	57	3,5%
Moderate	from 0,32 to 0,49	20	9	29	31,0%
High	from 0,49 to 0,66	6	14	20	70,0%
Veri high	from 0,66	2	53	55	96,4%

Low risk
 Moderate risk
 High risk
 High risk

many scores, calculators and RAM for venous thrombosis. The most famous RAMs are: 4-Element RAM, Caprini RAM, the full logistic model, Geneva RISK Score, IMPROVE-RAM, Kucher Model, Multivariable Model, Padua Prediction Score, QThrombosis Risk Calculator. Ideal RAM should be tested by external studies to identify patients with high VTE risk, improve thromboprophylaxis and outcomes, and be cost-effective [10]. It should not contain too many criteria and should be easily applicable in clinical practice [11]. None of the current RAMs meets these criteria [10]. Potential limitations of most RAMs include the lack of prospective validation, applicability only to high-risk subgroups, and high complexity of use [12].

Almost all RAMs included factors such as a history of VTE, prolonged immobilization, central venous catheter, cancer, old age, trauma, surgery, hormone replacement therapy or oral contraceptives. Arterial thrombosis as risk factor is taken into account in the Caprini RAM, Geneva Risk Score and Padua Prediction Score. Concomitant pathologies such as HF, COPD, and inflammatory diseases of the joints and intestine were taken into account in the Caprini RAM, Geneva Risk Score, Padua Prediction Score, and Multivariable Model. Obesity (BMI >30) considered as a risk factor in each RAM, except for IMPROVE-RAM and 4-Element RAM. The Caprini RAM assessed the presence of thrombophilia, such as factor V Leiden and prothrombin G20210A mutations, high homocysteine level, and lupus anticoagulant [10]. Padua Prediction Score took into account deficiency of antithrombin, proteins C or S, as well as factor V Leiden and prothrombin G20210A mutations [13];

IMPROVE-MPP — deficiency of antithrombin, proteins C or S, factor V Leiden and prothrombin G20210A mutations, and antiphospholipid syndrome [14]. The presence of thrombophilia was also assessed in the Geneva Risk Score and Multivariable Model [10].

External testing was carried out by Padua Prediction Score, Geneva Risk Score, Kucher Model, where thromboprophylaxis appointment improvement was shown [15]. In prospective studies, only Geneva Risk Score, Padua Prediction Score, and IMPROVE-RAM were assessed.

We developed a calculator taking into account both known risk factors, and congenital thrombophilia and concomitant pathology. The thromboprophylaxis should be considered at high individual risk (>0,45) of venous thrombosis. According to our truncated RAM version, patients without diagnosed thrombophilia and with moderate venous thrombosis risk needs thrombophilia screening to clarify the risk

Conclusion

The advantages of our RAM are a small number of factors necessary for assessing the risk, considering of four thrombophilias and online access. Unfortunately, our RAM has some limitations. Our monocentric study included a small number of patients. Despite this, the obtained formula showed a high forecast accuracy and clinical value. However, to verify the effectiveness of our RAM, an external prospective study is necessary. We believe that this RAM will help practitioners solve problems with thromboprophylaxis and minimize errors.

Conflicts of Interest: nothing to declare.

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